

Cannabinoid Hyperemesis Relieved by Compulsive Bathing

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Cannabinoid hyperemesis is a clinical syndrome characterized by repeated vomiting and associated learned compulsive hot water bathing behavior due to long-term marijuana use. Research has identified type 1 cannabinoid receptors in the intestinal nerve plexus that have an inhibitory effect on gastrointestinal motility. This inhibitory effect may lead to hyperemesis in marijuana users. The thermoregulatory role of endocannabinoids may be responsible for the patient's need to take hot showers. We report 2 cases of cannabinoid hyperemesis that demonstrate this unusual adverse effect of marijuana use.

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CB1 = cannabinoid type 1; CT = computed tomography

Cannabis is one of the most widely used illicit drugs in the United States. The prevalence of past-year cannabis use disorders has increased to 3 million cases during the past decade,¹ with a lifetime prevalence of 7.2% in adults.² In 2004, Allen et al³ reported a syndrome called cannabinoid hyperemesis in South Australia. Symptoms in long-term marijuana users included intractable vomiting that was unresponsive to antiemetics and associated with learned compulsive bathing behavior. Treatment was supportive care with intravenous fluids for 24 to 48 hours; symptoms resolved when patients stopped using cannabis. We report 2 cases of cannabinoid hyperemesis that, to our knowledge, are the first to be reported in the United States. Our goal is to increase awareness of this unusual adverse effect of marijuana use.

REPORT OF CASES

CASE 1

An obese 25-year-old woman who was a long-term cannabinoid user presented to the emergency department with nausea, vomiting, and abdominal pain that worsened for several days. During the previous 5 years, the patient had noted intermittent episodes of similar symptoms, each lasting about a week and often requiring hospitalization for dehydration. Her symptoms were refractory to all types of antiemetic medications and only responded to prolonged hot showers, some lasting 6 hours or more. Her medical history included bipolar disorder, reflux esophagitis, polycystic ovarian disease, and mild cerebral palsy with chronic mild left facial droop. She had no history of surgery or known drug allergies and reported that she took only lamotrigine. She had begun smoking marijuana 6 to 7 years earlier and used the substance almost daily. Her last mari-

juana use was 1 day before admission to the hospital. She denied alcohol, tobacco, or other illicit drug use.

On physical examination, the patient's vital signs included a temperature of 36.9°C, a pulse of 74 beats/min, a respiratory rate of 20 breaths/min, a blood pressure of 110/80 mm Hg, and an oxygen saturation of 98% while breathing room air. She was in moderate distress and found to be writhing in bed. She had a mild left facial droop, her pupils were equal and reactive to light, and extraocular movements were intact. She had moist mucous membranes. There was no lymphadenopathy or thyromegaly. Results of a cardiovascular examination were normal, and her chest was clear. The abdomen was soft and diffusely tender with decreased bowel sounds and no rebound or guarding. No organomegaly was detected. Examination of her extremities revealed no edema, cyanosis, or clubbing. Although findings on neurologic examination were largely unremarkable, a detailed examination was not possible because of her inability to cooperate secondary to abdominal discomfort and requests to take a shower.

Laboratory studies showed mild leukocytosis; her white blood cell count of $14.0 \times 10^9/L$ (reference range, $3.5\text{--}10.5 \times 10^9/L$) transiently increased to $17.0 \times 10^9/L$ later that day, only to fall to $9.8 \times 10^9/L$ on the next day without further intervention. Pregnancy test results were negative, and findings on a complete metabolic panel, including liver function and amylase, lipase, and thyroid-stimulating hormone tests, were normal. The patient's urine toxicology test was positive for cannabinoid. Past investigations of her symptoms included abdominal radiography, computed tomography (CT) of the head, CT of her abdomen and pelvis without contrast medium, cholescintigraphy (hepatobiliary iminodiacetic acid scan), 2 gastric emptying studies, modified barium swallow, abdominal ultrasonography, and esophagogastroduodenoscopy. Findings on all studies were normal, except for the initial gastric emptying study, which showed delayed gastric emptying that normalized after 3 days. On this admission, the patient again underwent CT of her abdomen and pelvis; findings were unremarkable.

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The patient was admitted for supportive care because she could not tolerate food. Many antiemetic medications, including ondansetron, promethazine, metoclopramide, lorazepam, and esomeprazole, were given with minimal symptomatic relief. Morphine sulfate was given for abdominal pain. Erythromycin was ordered to help increase gastric motility, but its administration was unsuccessful because the patient refused to leave the hot shower in her room. Indeed, she spent much of her hospitalization in the shower, noting that this was the only thing that controlled her symptoms. She showered as much as 4 hours at a time and even left her room to use a neighbor's shower when her shower stall broke. Her symptoms resolved in 48 hours without any other intervention, and she was discharged from the hospital.

CASE 2

A 23-year-old man presented with 1 day of nausea, vomiting, and abdominal pain in the epigastric and right upper quadrant. His symptoms were worsened by food and improved with a prolonged hot shower. He noted having similar symptoms several times during the past 2 years; on these occasions, he would come to the emergency department only after exhausting all the hot water in his shower at home. He reported no fevers, chills, indigestion, travel history, or sick contacts. He had experienced chronic abdominal pain for 9 years and had been tested for human immunodeficiency virus and, more recently, for tuberculosis, with negative findings on both. He had no known drug allergies and was not taking any medications. He reported using marijuana 2 to 3 times a day for the past 9 years but denied alcohol or other illicit drug use.

On physical examination, the patient's vital signs included a temperature of 36.6°C, a pulse of 86 beats/min, a blood pressure of 140/100 mm Hg, and a respiratory rate of 18 breaths/min. He was not in acute distress. His skin was warm and well perfused. His mucous membranes were moist, his pupils were equal and reactive to light, and his extraocular movements were intact. His neck was supple without thyromegaly. Findings on cardiovascular examination and examination of his extremities were unremarkable, and his chest was clear. His abdomen was soft, nondistended, and tender.

His laboratory values revealed mild leukocytosis (white blood cell count, $12.4 \times 10^9/L$; 50% neutrophils). Test results on urinalysis, hepatitis serologies, and complete metabolic panel, including liver function, amylase, and lipase tests, were normal. Findings were also negative on a perinuclear-staining antineutrophil cytoplasmic antibody test and for tests for cytomegalovirus and human immunodeficiency virus. Previously completed imaging studies, including abdominal radiography, CT of the abdomen and

pelvis without contrast medium, CT of the head without contrast medium, abdominal ultrasonography, esophago-gastroduodenoscopy, and colonoscopy, yielded normal results. Findings on repeated CT of his abdomen and pelvis with contrast medium at the time of this presentation were normal.

The patient noted feeling better soon after coming to the emergency department. He stated that he had come to the hospital because he was afraid his symptoms would not improve and because he had used all the hot water in his house by showering for 4 hours. He was treated symptomatically with ondansetron and phenergan for nausea, dilaudid for pain control, and normal saline for hydration. After a few hours, his symptoms resolved, and he was discharged from the hospital.

DISCUSSION

Cannabinoid hyperemesis, an often unrecognized adverse effect of marijuana use, is characterized by repeated vomiting without an obvious organic cause and learned compulsive bathing behavior. The symptoms resolve in 24 to 48 hours with conservative management and cessation of marijuana use. Both patients about whom we report here exhibited these outcomes.

The mechanism of cannabinoid hyperemesis is unknown. Marijuana, whether taken as a pill or smoked, has been used to treat chemotherapy-induced nausea and vomiting, glaucoma, anorexia, anxiety, and for purposes of muscle relaxation. Some known adverse reactions include altered sensorium, blurred vision, decreased coordination, dry mouth and eyes, hypotension or hypertension, sedation, somnolence, rash, urinary retention,⁴ and nausea and vomiting.⁵ Marijuana is being used for its antiemetic and appetite-stimulating properties in certain patients; paradoxically, however, it can cause nausea and vomiting with abdominal pain in some patients.

Possible mechanisms of cannabinoid hyperemesis include toxicity resulting from marijuana's long half-life, its lipophilic properties, its ability to delay gastric emptying, its dysregulation of thermoregulatory and autonomic equilibrium through its effect on the limbic system, and the binding of cannabinoids to cannabinoid type 1 (CB1) receptors in the brain.³ Vomiting is coordinated by the brainstem in response to noxious stimuli involving many neurotransmitters, including neurokinin, serotonin, and vasopressin.⁶ Metoclopramide, a commonly used antiemetic, acts as an antagonist to the same chemoreceptor trigger zone in the brainstem opposing the vomiting reflex. It also increases gastric motility, thereby further decreasing the emetic response.^{6,7} Two types of cannabinoid receptors have been identified in the human brain. The CB1 receptors

have a neuromodulatory role and are found in the central nervous system and intestinal nerve plexus.⁸ Cannabinoid type 2 receptors, which are typically found in nonneuronal tissues but which are also present in microglia, have an immunomodulatory effect.⁹ Marijuana and its derivatives, such as nabilone and dronabinol, have been used as antiemetics and appetite stimulants in patients undergoing chemotherapy or those with AIDS. The antiemetic action of the cannabinoids appears to be centrally mediated.⁸ However, the mechanism underlying the emetic properties of marijuana is unknown. Acute toxicity from intravenous injection of marijuana has been reported to cause severe vomiting and diarrhea in humans¹⁰ and in ferrets injected with 2-arachidonoylglycerol, a potent cannabinoid agonist.¹¹ One explanation could be that cannabinoids depress peristalsis, intestinal passage of materials, and intestinal contraction in a dose-dependent manner.^{12,13} In patients who develop hyperemesis, the peripheral effects could override the centrally mediated antiemetic effects of cannabinoids.

The learned compulsive bathing behavior exhibited by these patients is another notable characteristic of cannabinoid hyperemesis. The endocannabinoid system plays a role in the modulation of neuroendocrine function by way of the CB1 receptors of the hypothalamus-pituitary-adrenal axis.¹⁴ The role of the hypothalamus in regulating body temperature is well known.¹⁵ More recently, the hypothalamus has been reported to serve as a location for integrating central and peripheral thermosensory input.¹⁶ Subjective thermoregulatory sensation could initiate the need to act, or in this case, to take a hot shower. We propose 2 potential mechanisms of action for this compulsive bathing behavior. First, the brain may react to changes in core body temperature due to the dose-dependent hyperthermic effects of delta-9-tetrahydrocannabinol (the psychoactive component of cannabinoid).¹⁷ Second, the behavior observed (seeking warmer skin temperature) may be a result of direct CB1 receptor activation in the hypothalamus by delta-9-tetrahydrocannabinol or another active compound and may not necessarily be a response to changes in core body temperature.

CONCLUSION

The toxicity and adverse consequences of long-term marijuana use are still under investigation. Marijuana may either cause or control nausea and vomiting, but the mechanism is unknown. Given the prevalence of illicit marijuana use and the increased popularity of marijuana use for medicinal purposes, these paradoxical effects require further

investigation. This case report aims to raise awareness of the potential adverse effects of marijuana use and the importance of obtaining a thorough patient history, which should include consideration of the potential for substance abuse. A thorough history is particularly important when a patient presents with intractable nausea and vomiting that are refractory to antiemetic medication but that are relieved by a hot shower. When confronted with these unusual symptoms, the physician should consider not only organic disease but also illicit marijuana use as a possible cause.

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